General

Guideline Title

VA/DoD clinical practice guideline for the management of chronic multisymptom illness.

Bibliographic Source(s)

Management of Chronic Multisymptom Illness Guideline Working Group. VA/DoD clinical practice guideline for the management of chronic multisymptom illness. Washington (DC): Department of Veteran Affairs, Department of Defense; 2014 Oct. 89 p. [143 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Management of Medically Unexplained Symptoms: Chronic Pain and Fatigue Working Group. VHA/DoD clinical practice guideline for the management of medically unexplained symptoms: chronic pain and fatigue. Washington (DC): Veterans Health Administration, Department of Defense; 2001 Jul. Various p. [148 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- March 22, 2016 – Opioid pain medicines : The U.S. Food and Drug Administration (FDA) is warning about several safety issues with the entire class of opioid pain medicines. These safety risks are potentially harmful interactions with numerous other medications, problems with the adrenal glands, and decreased sex hormone levels. They are requiring changes to the labels of all opioid drugs to warn about these risks.

Recommendations

Major Recommendations

Note from the Department of Veterans Affairs and the Department of Defense (VA/DoD) and the National Guideline Clearinghouse

(NGC): The recommendations for the management of chronic multisymptom illness (CMI) are organized into 6 modules (including diagnosis/evaluation, management strategies, and 3 therapeutic intervention modules) with 1 algorithm. The modules with accompanying recommendations are presented below. See the original guideline document for the algorithm and evidence tables associated with selected recommendations, including level and quality of evidence, strength of recommendation, and supporting evidence citations.

The strength of recommendation grading (Strong For, Weak For, Strong Against, Weak Against) is defined at the end of the "Major Recommendations" field.

Diagnosis and Evaluation

1. The guideline panel recommends that all patients receive a thorough evaluation of symptoms based on clinical judgment. (Strong For)
2. This guideline panel recommends against the use of any test for which there may be limited additional benefit to confirm the diagnosis of CMI. Testing for rare exposures or biologic effects should only be done in the presence of supportive history or physical findings. (Strong Against)
3. This guideline panel suggests discussing risk factors using principles of health risk communication within a therapeutic patient-provider alliance for those patients who wish to further understand factors that could contribute to their condition. (Weak For)

Management Strategies

4. The guideline panel recommends using a collaborative, team-based approach, including a behavioral health specialist, for the primary care management of patients with CMI. (Strong For)
5. The guideline panel recommends that the healthcare team use shared decision making principles to develop a comprehensive and personalized treatment plan in the care and management of patients with CMI. (Strong For)
6. The guideline panel suggests that all providers involved in the care of patients with CMI enhance their knowledge of the following critical domains:
    - Communication skills (e.g., active listening, risk communication/perception)
    - Empathy skills
    - Working with interdisciplinary teams
    - The biopsychosocial model
    - Risk factors for CMI and analogous conditions
    - Military cultural competency
    - Deployment related exposures

    (Weak For)

Therapeutic Interventions for Global CMI

7. The guideline panel suggests incorporating appropriate elements of physical activity as part of a comprehensive and integrated treatment plan for patients with CMI. (Strong For)
8. The guideline panel recommends offering cognitive behavioral therapy, delivered by trained professionals, for patients with CMI. (Strong For)
9. The guideline panel recommends considering mindfulness-based therapy, reattribution, behavioral medical intervention, and/or brief psychodynamic interpersonal psychotherapy, delivered by trained professionals, for patients with CMI. (Weak For)
10. The guideline panel recommends considering complementary and integrated medicine interventions as a component of personalized, proactive patient-driven care in the management of patients with CMI. (Weak For)
11. The guideline panel suggests considering a trial of selective serotonin reuptake inhibitor (SSRI), serotonin–norepinephrine reuptake inhibitor (SNRI), or mirtazapine for the treatment of clinical symptoms of CMI. (Weak For)
12. The guideline panel suggests against the use of doxycycline for the treatment of patients with clinical symptoms of CMI. (Weak Against)
13. The guideline panel recommends against the long-term use of opioid medications for the management of patients with CMI. (Strong Against)

Therapeutic Interventions for Pain-Predominant CMI

14. The guideline panel suggests considering acupuncture as part of the management of patients with pain-predominant symptoms of CMI. (Weak For)
15. The guideline panel suggests considering non-steroidal anti-inflammatory drugs (NSAID) for treating certain peripheral pain symptoms associated with CMI, though they do not necessarily lead to global beneficial effect. (Weak For)
16. The guideline panel suggests considering tramadol for treating certain pain symptoms associated with CMI that fail to respond to other nonopioid analgesic medications or non-pharmacologic approaches. (Weak For)

17. The guideline panel suggests a trial of SNRI for the treatment of patients with clinical symptoms of pain-predominant CMI. (Weak For)
18. The guideline panel suggests considering a trial of tricyclic antidepressants (TCA), SSRI, or pregabalin (PGB) for the treatment of patients with clinical symptoms of pain-predominant CMI. (Weak For)

Therapeutic Interventions for Fatigue-Predominant CMI

19. The guideline panel recommends considering acupuncture as part of the management of patients with fatigue-predominant symptoms of CMI. (Weak For)
20. The guideline panel suggests considering a trial of SNRI or TCA for patients with clinical symptoms of fatigue predominant CMI. (Weak For)
21. The guideline panel suggests against the use of pharmacologic agents for sleep disturbances in CMI. (Weak Against)
22. The guideline panel suggests against the use of stimulants for the treatment of fatigue-predominant CMI. (Weak Against)
23. The guideline panel recommends against the empiric use of antivirals or antibiotics for the treatment of fatigue-predominant CMI. (Strong Against)
24. The guideline panel recommends against the use of corticosteroids for the treatment of fatigue-predominant CMI. (Strong Against)
25. The guideline panel recommends against the use of immunotherapy for the treatment of the symptoms of fatigue predominant CMI. (Strong Against)

Therapeutic Interventions for Gastrointestinal-Predominant CMI

26. The guideline panel suggests treating patients with CMI and predominantly gastrointestinal symptoms, in accordance with recognized evidence-based care for irritable bowel syndrome (IBS). (Weak For)
27. The guideline panel recommends considering minimal contact psychological therapies for treatment of gastrointestinal-predominant CMI. (Weak For)
28. The guideline panel suggests against the use of acupuncture for treatment of patients with gastrointestinal-predominant symptoms of CMI. (Weak Against)

Definitions:

The relative strength of the recommendation is based on a binary scale, "Strong" or "Weak." A strong recommendation indicates that the Work Group is highly confident that desirable outcomes outweigh undesirable outcomes. If the Work Group is less confident of the balance between desirable and undesirable outcomes, they present a weak recommendation.

Similarly, a recommendation for a therapy or preventive measure indicates that the desirable consequences outweigh the undesirable consequences. A recommendation against a therapy or preventive measure indicates that the undesirable consequences outweigh the desirable consequences.

The grade of each recommendation is presented as part of a continuum:

- Strong For (or "The guideline panel recommends offering this option …")
- Weak For (or "The guideline panel suggests offering this option …")
- Weak Against (or "The guideline panel suggests not offering this option …")
- Strong Against (or "The guideline panel recommends against offering this option …")

Note that weak (For or Against) recommendations may also be termed "Conditional," "Discretionary," or "Qualified." Recommendations may be conditional based upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented. Recommendations may be at the discretion of the patient and clinician or they may be qualified with an explanation about the issues that would lead decisions to vary.

Clinical Algorithm(s)

An algorithm designed to facilitate clinical decision making for the management of chronic multisymptom illness (CMI) is provided in the original guideline document.

Scope

Disease/Condition(s)

Chronic multisymptom illness (CMI)

Guideline Category

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Family Practice

Gastroenterology

Internal Medicine

Nursing

Psychiatry

Psychology

Intended Users

Advanced Practice Nurses

Health Care Providers

Nurses

Physician Assistants

Physicians

Psychologists/Non-physician Behavioral Health Clinicians

Guideline Objective(s)

- To assist primary care providers in treating and managing patients with chronic multisymptom illness (CMI)
- To provide primary care clinicians with a framework by which to evaluate the individual needs and preferences of patients who may be experiencing CMI or medically unexplained symptoms, leading to improved clinical outcomes

Target Population

Adult patients who may be experiencing chronic multisymptom illness (CMI)

Note: The recommendations within this guideline were developed with a focus on individuals who are eligible for care in the Veterans Health Administration or the Department of Defense healthcare delivery system. It includes deployed and non-deployed Veterans as well as active Service Members. This guideline does not provide recommendations for the treatment of CMI in children or adolescents.

Interventions and Practices Considered

Diagnosis/Evaluation

1. Thorough evaluation of symptoms based on clinical judgment
2. Testing for rare exposures or biologic effects (only in the presence of supportive history or physical findings)
3. Discussing risk factors using principles of health risk communication within a therapeutic patient-provider alliance

Management/Treatment

1. Using a collaborative, team-based approach, including a behavioral health specialist, for primary care management
2. Use of shared decision making principles to develop a comprehensive and personalized treatment plan

Therapeutic Interventions for Global Chronic Multisystem Illness (CMI)

1. Physical activity
2. Cognitive behavioral therapy
3. Mindfulness-based therapy, reattribution, behavioral medical intervention, and/or brief psychodynamic interpersonal psychotherapy
4. Complementary and integrated medicine interventions
5. Selective serotonin reuptake inhibitor (SSRI), serotonin–norepinephrine reuptake inhibitor (SNRI), or mirtazapine

Therapeutic Interventions for Pain-Predominant CMI

1. Acupuncture
2. Non-steroidal anti-inflammatory drugs (NSAID)
3. Tramadol
4. SNRI
5. Tricyclic antidepressants (TCA), SSRI, or pregabalin (PGB)

Therapeutic Interventions for Fatigue-Predominant CMI

1. Acupuncture
2. SNRI or TCA

Therapeutic Interventions for Gastrointestinal-Predominant CMI

1. Use of recognized evidence-based care for irritable bowel syndrome (IBS)
2. Minimal contact psychological therapies

Note: The following interventions were considered but not recommended:

Any test for which there may be limited additional benefit to confirm the diagnosis of CMI
Doxycycline
Long-term use of opioid medications
Pharmacologic agents for sleep disturbances
Stimulants
Empiric use of antivirals or antibiotics
Corticosteroids
Immunotherapy
Acupuncture for gastrointestinal-predominant CMI

Major Outcomes Considered

- Reduction in the intensity or frequency of symptoms (e.g., pain, fatigue)
- Improved function
- Improved quality of life
- Health care use
- Harms

- Identification of organic disease patterns or a change in treatment/management strategy
- Degree of association of risk factors with chronic multisymptom illness (CMI)

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Formulating Evidence Questions

The Clinical Practice Guideline (CPG) Champions were tasked with identifying key evidence questions to guide the systematic review of the literature on chronic multisymptom illness (CMI). These questions, which were developed in consultation with the Lewin Group's evidence review team, addressed clinical topics of the highest priority for the Veterans Affairs (VA) and Department of Defense (DoD) populations. The key questions follow the population, intervention, comparison, outcome, timing and setting (PICOTS) framework for evidence questions, as established by the Agency for Healthcare Research and Quality (AHRQ). Table A-1 in the original guideline document provides a brief overview of the PICOTS typology.

The Champions and evidence review team carried out several iterations of this process, each time narrowing the scope of the CPG and the literature review by prioritizing the topics of interest. Table A-2 in the original guideline document contains the final set of key questions used to guide the systematic review for this CPG.

See Appendix A in the original guideline document for information on population, interventions, and outcomes that helped form the key questions.

Conducting Systematic Literature Review

The methods of the systematic review are described below. In part, these methods followed the guidelines for conducting a systematic review set forth by AHRQ in the "Methods Guide for Effectiveness and Comparative Effectiveness Reviews." Additionally, the methods followed the guidance set forth by the VA/DoD in the *Guideline for Guidelines* document (see the "Availability of Companion Documents" field).

For all key questions, the following external and internal databases were searched: MEDLINE, EMBASE (via the OVID SP platform using the one-search and de-duplication features), the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment Database. Searches were designed to identify unique reviews, trials, and technology assessments. Searches of the World Wide Web were also performed to capture relevant grey literature that had not been indexed to the databases listed previously. The searches covered the time period of January 2000 through October 2013. The search strategy was based on a combination of Medical Subject Headings (MeSH) terminology and text key words, and can be found in Table A-3 in the original guideline document.

The literature searches identified 6,624 citations potentially addressing the key questions of interest. Of those, 4,295 were excluded upon title review for clearly not meeting inclusion criteria (e.g., not pertinent to the topic, not published in English, published prior to study inclusion publication date, or not a full-length article). Overall, 2,329 abstracts were reviewed with 1,426 of those being excluded for the following reasons: not a systematic review or clinical study, did not address a key question of interest to this review, did not enroll population of interest, or published prior to January 2000. A total of 903 full-length articles were reviewed. Of those, 419 were excluded at a first pass review for the following: not addressing a key question of interest, not enrolling the population of interest, not meeting inclusion criteria for clinical study or systematic review, not enrolling sufficient patients for key question 1 or 10-12, or being a duplicate. A total of 484 full-length articles were thought to address one or more key questions and were further reviewed. Of these, 381 were ultimately excluded. Reasons for their exclusion are presented in Figure A-1 of the original guideline document.

Criteria for Study Inclusion/Exclusion

General Criteria

- Clinical studies published on or after January 1, 2000, and systematic reviews of associated symptom based syndromes (i.e., fibromyalgia,

chronic fatigue syndrome, and functional gastrointestinal disorders) published on or after January 1, 2008.
- Studies must have been published in English.
- Publication must have been a full clinical study or systematic review; abstracts alone were not included. Similarly, letters, editorials, and other publications that were not full-length, clinical studies were not accepted as evidence.
- Study must have enrolled a patient population in which at least 85% of patients had CMI or associated condition or symptoms.
- Studies enrolled adults 18 years or older. In studies that mixed adults and children, at least 85% of the enrolled patients had to be 18 years or older.
- Studies that enrolled adults with single symptoms or multiple symptoms of less than 6 months duration were excluded.

Diagnosis/Evaluation Studies

- Studies must have evaluated a diagnostic test within an active or inactive military population (e.g., this included studies of Gulf War ill Veterans versus Gulf War well or civilian or non-Gulf War Veterans). Studies considering non-military populations with symptom-based syndromes such as fibromyalgia syndrome, chronic fatigue syndrome, or irritable bowel syndrome were excluded.
- Study must have been a case control or comparative study that compared diagnostic technology evaluation versus clinical evaluation or different diagnostic technologies.
- Studies must have enrolled ≥50 patients with at least 10 patients enrolled per study group.
- Studies must have considered diagnostic tests within the following categories: biomarkers (this included studies of biological markers and neuroimaging studies), neuropsychological test batteries, and sleep studies (studies were excluded if they considered only questionnaires or checklists to distinguish populations).

Treatment and Management Studies

- Study must have evaluated a treatment or management strategy for CMI.
- Study must have been a prospective, randomized or nonrandomized comparative trial with an independent control group.
- Crossover trials were considered only if data from the first treatment period were reported separately.
- Study must have enrolled ≥10 patients per treatment arm.
- The study must have reported data on at least one of the included outcomes.
- Study must have followed patients for at least 4 weeks.
- All subjective outcomes (e.g., pain, aspects of patient function) must have been measured using validated instruments.
- For associated symptom based syndromes, such as fibromyalgia, chronic fatigue syndrome, and irritable bowel syndrome, only systematic reviews published from 2008 till present that evaluated a treatment strategy were included as evidence in the review.

Risk Factor Studies

- Study must have been a case controlled or a comparative study that compares patients with CMI to another population of patients (e.g., CMI versus Major Depression) or compared patients with CMI who had a risk factor(s) to patients who did not have the factor(s).
- Study must have enrolled ≥500 patients.
- Study must have investigated risk factors for predisposing, precipitating, or perpetuating CMI. Expert opinion papers were not considered as evidence addressing the referral questions.

See Table A-3 in the original guideline document for more details of the literature search strategies.

The systematic review conducted for this CPG examined literature that was published up to February 2014. The Work Group recognizes that several new studies have been published since that time. Consequently, the group reviewed and incorporated new evidence in developing and refining the recommendations, as long as the studies met all *a priori* inclusion criteria for the systematic review.

Number of Source Documents

103 studies addressed one or more of the Key Questions and were considered as evidence in the systematic review. See Figure A-1 in the original guideline document for a systematic review flow diagram.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence and Definitions*

High quality — Further research is very unlikely to change confidence in the estimate of effect.
Moderate quality — Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low quality — Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very low quality — Any estimate of effect is very uncertain.

*Guyatt, G. H., Oxman, A. D., Vist, G. E., Kunz, R., Falck-Ytter, Y., Alonso-Coello, P., Schünemann, H. J. & the GRADE Working Group. (2008). GRADE; An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ, 336*, 924-926.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Abstracting and Managing Data

For each study included in the systematic literature review, the evidence review team abstracted the following study level details: country, purpose, and quality rating. For previous systematic reviews, the team reported the search strategy used, study selection criteria, and overall information about the evidence base, including number of included studies and overall patients enrolled. For all studies, the team abstracted data about characteristics of the included patients and interventions being assessed.

Assessing Individual Studies' Methodological Quality (i.e., Internal Validity or Risk of Bias)

As per the Department of Veterans Affairs/Department of Defense (VA/DoD) *Guidelines for Guidelines* document (see the "Availability of Companion Documents" field), risk-of-bias (or study quality) of individual studies and previous systematic reviews was assessed using the U.S. Preventive Services Task Force (USPSTF) method. Each study was assigned a rating of Good, Fair, or Poor based on sets of criteria that vary depending on study design. Detailed lists of criteria and definitions of Good, Fair, or Poor ratings for different study designs appear in Appendix VII of the USPSTF procedure manual.

Data Synthesis

The evidence review team used a narrative approach to synthesizing the evidence for all the Key Questions. As indicated in the VA/DoD *Guidelines for Guidelines* document, the first line of evidence was previous systematic reviews. For questions in which a previous review was available, individual studies that met this review's inclusion criteria were used to supplement or update the previous review. The evidence review team considered whether subsequent evidence supports the conclusions reported in the previous review. For questions for which no previous review was available, the team summarized the overall findings for the outcomes of interest of the studies that addressed a key question.

Assessing the Overall Quality of the Body of Evidence for an Outcome

The overall quality of the body of evidence supporting the findings for the outcomes of interest in this report was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. The GRADE system primarily involves consideration of the following factors: overall study quality (or overall risk of bias or study limitations), consistency of evidence, directness of evidence, and precision of evidence. Given time and resources, other factors such as publication bias may also be considered. For more information on the GRADE system go to the GRADE working group website at the following link: http://www.gradeworkinggroup.org/.

The GRADE system rates the overall quality of the evidence as High, Moderate, Low, and Very Low. The overall quality of a body of evidence is rated based on the factors described above. For instance, a body of evidence that consists of randomized controlled trials (RCTs) automatically

starts with a rating of high quality. This rating can be downgraded if some of the RCTs have serious flaws such as lack of blinding of outcome assessors, not reporting concealment of allocation, or high dropout rate. Similarly, the quality can be downgraded or further downgraded if inconsistencies of findings are present or if there is a lack of precision surrounding an outcome's effect size.

Assessing Applicability

When describing the evidence base addressing a Key Question, the evidence review team discussed aspects of the included studies, such as characteristics of included patients and treatments being assessed that may make the overall findings of the studies more or less applicable to the population, treatments, or outcomes of interest to this review.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The methodology used in developing the 2014 Chronic Multisymptom Illness Clinical Practice Guideline (CMI CPG) follows the *Guideline for Guidelines,* an internal document of the Department of Veterans Affairs (VA) and Department of Defense (DoD) Evidence-Based Practice Working Group (EBPWG) (see the "Availability of Companion Documents" field). This document provides information regarding the process of developing guidelines, including the identification and assembly of the Guideline Champions (Champions) and other subject matter experts from within the VA and DoD, known as the Work Group, and ultimately, the submission of an updated CMI CPG.

The Champions and Work Group for this CPG were charged with developing evidence-based clinical practice recommendations and publishing a guideline document to be used by providers within the VA/DoD healthcare system. Specifically, the Champions for this guideline were responsible for identifying the key questions of greatest clinical relevance, importance, and interest for the management and treatment of patients with CMI. In addition, the Champions assisted in:

1. Conducting the evidence review, including providing direction on inclusion and exclusion criteria
2. Assessing the level and quality of the evidence
3. Identifying appropriate disciplines to be included as part of the Work Group
4. Directing and coordinating the Work Group
5. Participating throughout the guideline development and review processes

The VA Office of Quality, Safety and Value, in collaboration with the Medical Command of the DoD, identified four clinical leaders as Champions for the 2014 CMI CPG.

The Lewin Team (Team), including DutyFirst Consulting and ECRI Institute, was contracted by VA and DoD to support the development of this CPG and conduct the evidence review. The Team held the first conference call in May 2013, with participation from the contracting officer's representatives (COR), leaders from the VA and DoD evidence-based guideline development program, and the Champions. During this call, the project team discussed the scope of the guideline initiative, the roles and responsibilities of the Champions, the project timeline, and the approach for developing specific research questions on which to base a systematic review about the management of CMI. The group also identified a list of clinical specialties and areas of expertise that are important and relevant to the treatment and management of CMI, from which the Work Group members were recruited. The specialties and clinical areas of interest included Clinical Dietetics, Family Medicine, Healthcare Systems Management and Policy, Internal Medicine, Gastroenterology, Neurology, Nursing, Pharmacy Benefit Management, Physical Therapy, Psychiatry, Psychology and Surgery.

The guideline development process for the 2014 CMI CPG consisted of the following steps:

- Formulating evidence questions (key questions)
- Conducting the systematic review
- Convening a two and a half day face-to-face meeting with the CPG Champions and Work Group members
- Drafting and submitting a final CPG on the management of CMI to the VA/DoD EBPWG

Appendix A in the original guideline document provides a detailed description of each of these tasks.

Convening the Face-to-Face Meeting

In consultation with the Contracting Officer Representative, the Champions, and the Work Group, the Lewin Team convened a three and a half day face-to-face meeting of the CPG Champions and Work Group members on January 14-17, 2014. These experts were gathered to develop and draft the clinical recommendations for an update to the 2001 CPG. Lewin presented findings from the evidence review of the key questions in order to facilitate and inform the process.

Under the direction of the Champions, the Work Group members were charged with interpreting the results of the evidence review, and asked to retain, revise, or reject each recommendation from the 2001 CPG. In addition, members developed new clinical practice recommendations, not presented in the 2001 CPG, based on the 2013 evidence review. At this meeting, Work Group members were assigned to one of four smaller subgroups depending on their area of clinical expertise.

Grading Recommendations

This CPG uses the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology to assess the quality of the evidence base and assign a grade for the strength for each recommendation. The GRADE system uses the following four domains to assess the strength of each recommendation:

- Balance of desirable and undesirable outcomes
- Confidence in the quality of the evidence
- Values and preferences
- Other implications, as appropriate, e.g.,:
    - Resource Use
    - Equity
    - Acceptability
    - Feasibility
    - Subgroup considerations

Refer to the original guideline document for further descriptions of each domain.

Table A-4 in the original guideline document ("Evidence to Recommendations Framework") was used by the Work Group to guide discussions on each domain.

The strength of a recommendation is defined as the extent to which one can be confident that the desirable effects of an intervention outweigh its undesirable effects and is based on the framework above, which combines the four domains.

The GRADE of a recommendation is based on the following elements:

- Four decision domains used to determine the strength and direction (described above)
- Relative strength (Strong or Weak)
- Direction (For or Against)

Drafting and Submitting the Final CPG

Following the face-to-face meeting, the Champions and Work Group members were given writing assignments for the update of specific sections of the 2001 CPG that would form the narrative text for the 2014 CPG. During this time, the Champions also revised the 2001 algorithms and identified the content for the guideline summary and pocket card, as part of the provider toolkits that will be developed by the EBPWG following the publication of the 2014 CPG. The chronic multisymptom illness CPG Champions and Work Group developed several drafts of the Guideline, submitting the final document to the VA/DoD EBPWG in October 2014.

Rating Scheme for the Strength of the Recommendations

The relative strength of the recommendation is based on a binary scale, "Strong" or "Weak." A strong recommendation indicates that the Work Group is highly confident that desirable outcomes outweigh undesirable outcomes. If the Work Group is less confident of the balance between desirable and undesirable outcomes, they present a weak recommendation.

Similarly, a recommendation for a therapy or preventive measure indicates that the desirable consequences outweigh the undesirable consequences. A recommendation against a therapy or preventive measure indicates that the undesirable consequences outweigh the desirable consequences.

Using these elements, the grade of each recommendation is presented as part of a continuum:

- Strong For (or "The Expert Panel recommends offering this option …")
- Weak For (or "The Expert Panel suggests offering this option …")
- Weak Against (or "The Expert Panel suggests not offering this option …")
- Strong Against (or "The Expert Panel recommends against offering this option …")

Note that weak (For or Against) recommendations may also be termed "Conditional," "Discretionary," or "Qualified." Recommendations may be conditional based upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented. Recommendations may be at the discretion of the patient and clinician or they may be qualified with an explanation about the issues that would lead decisions to vary.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

A thorough explanation of the guideline validation process and public comment is provided in the Department of Veterans Affairs and the Department of Defense (VA/DoD) *Guideline for Guidelines* document (see the "Availability of Companion Documents" field).

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting each recommendation is not specifically stated.

The recommendations are based on a systematic appraisal of the published evidence on the management of chronic multisymptom illness (CMI). Table A-2 in the original guideline document indicates the number and type of studies that addressed each of the key questions. The evidence included systematic reviews, case-control trials, and randomized controlled trials.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Formulation of an efficient and effective assessment of the patient's condition
- Optimal use of therapy to reduce symptoms and enhance functionality
- Minimization of preventable complications and morbidity
- Emphasize on the use of personalized, proactive, patient-driven care

Potential Harms

- A diagnostic label may sometimes unnecessarily cause a patient to define him or herself as ill, an effect that could be especially problematic in occupational health care settings. Other clinicians may shift their attention/prioritization of the individual's concerns in response to a label.

The potential risks and benefits of applying a particular diagnostic label to symptom clusters should be weighed by the clinician and discussed with the patient prior to applying such a label.

- The reported adverse effects of acupuncture in one meta-analysis were bruising, nausea, fainting, discomfort at the sites of needle insertions or simulated needle insertions, and temporary edema of the hand.
- The most common adverse effects of tramadol were nausea, dizziness, somnolence, and constipation. Tramadol should be used with some caution due to the possibility of typical opiate withdrawal symptoms with discontinuation and the risk of abuse and dependence. In addition, evidence suggests that tramadol increases the risk of serotonergic syndrome in patients. Providers should use caution and discuss with their patients some of the adverse events associated with the use of tramadol prior to prescribing this medication.
- The overall summary effect of six studies assessing the efficacy of Qigong as physical exercise reported pain and plantar fasciitis as adverse effects in one study.
- See Appendix B in the original guideline document for information on adverse effects of specific pharmacological interventions.

Contraindications

Contraindications

See Appendix B in the original guideline document for information on contraindications of specific pharmacological interventions.

Qualifying Statements

Qualifying Statements

- The Department of Veterans Affairs (VA) and the Department of Defense (DoD) guidelines are based upon the best information available at the time of publication. They are designed to provide information and assist decision-making. They are not intended to define a standard of care and should not be construed as one. Neither should they be interpreted as prescribing an exclusive course of management.
- This Clinical Practice Guideline (CPG) is based on a systematic review of both clinical and epidemiological evidence. Developed by a panel of multidisciplinary experts, it provides a clear explanation of the logical relationships between various care options and health outcomes while rating both the quality of the evidence and the strength of the recommendations.
- Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every healthcare professional making use of these guidelines is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation.
- These guidelines are not intended to represent TRICARE policy. Further, inclusion of recommendations for specific testing and/or therapeutic interventions within these guidelines does not guarantee coverage of civilian sector care. Additional information on current TRICARE benefits may be found at www.tricare.mil or by contacting your regional TRICARE Managed Care Support Contractor.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

Patient Resources

Pocket Guide/Reference Cards

Quick Reference Guides/Physician Guides

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Management of Chronic Multisymptom Illness Guideline Working Group. VA/DoD clinical practice guideline for the management of chronic multisymptom illness. Washington (DC): Department of Veteran Affairs, Department of Defense; 2014 Oct. 89 p. [143 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2002 Aug (revised 2014 Oct)

Guideline Developer(s)

Department of Defense - Federal Government Agency [U.S.]

Department of Veterans Affairs - Federal Government Agency [U.S.]

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Guideline Committee

Management of Chronic Multisymptom Illness Guideline Working Group

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Financial Disclosures/Conflicts of Interest

A hallmark of the Department of Veterans Affairs and the Department of Defense (VA/DoD) guidelines is their relative freedom from conflict of interest. Conflicts of interest faced by the VA/DoD Evidence-Based Practice Working Group (EBPWG) and the working groups that it charters to develop specific guidelines are handled based on the Veterans Health Administration (VHA) Handbook 1004.07 - Financial Relationships between VHA Health Care Professionals and Industry, which was signed October 21, 2009. All EBPWG meetings utilize the process of real-time verbal disclosure as required by VHA Handbook 1004.07 - Information for Members of VHA Decision Making and Advisory Groups.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Management of Medically Unexplained Symptoms: Chronic Pain and Fatigue Working Group. VHA/DoD clinical practice guideline for the management of medically unexplained symptoms: chronic pain and fatigue. Washington (DC): Veterans Health Administration, Department of Defense; 2001 Jul. Various p. [148 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the Department of Veterans Affairs (VA) Web site.

Print copies: Department of Veterans Affairs, Veterans Health Administration, Office of Quality and Performance (10Q), 810 Vermont Ave. NW, Washington, DC 20420.

Availability of Companion Documents

The following are available:

- VA/DoD clinical practice guideline for the management of chronic multisymptom illness. Clinician summary. Washington (DC): Department of Veterans Affairs, Department of Defense; 2014. 12 p. Electronic copies: Available from the Department of Veterans Affairs (VA) Web site .
- VA/DoD clinical practice guideline for the management of chronic multisymptom illness. Pocket card. Washington (DC): Department of Veterans Affairs, Department of Defense; 2014. 6 p. Electronic copies: Available from the VA Web site .
- Guideline for guidelines. Washington (DC): Department of Veterans Affairs; 2013 Apr 10. Electronic copies: Available from the VA Web site .
- Putting clinical practice guidelines to work in VHA. Washington (DC): Department of Veterans Affairs. 64 p. Electronic copies: Available from the VA Web site .

In addition, a pharmacotherapy chart is available in Appendix B of the original guideline document .

Print copies: Department of Veterans Affairs, Veterans Health Administration, Office of Quality and Performance (10Q) 810 Vermont Ave. NW, Washington, DC 20420.

Patient Resources

The following is available:

- VA/DoD clinical practice guideline for the management of chronic multisymptom illness. Patient summary. Washington (DC): Department of Veterans Affairs, Department of Defense; 2014. 4 p. Electronic copies: Available from the Department of Veterans Affairs (VA) Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI on February 12, 2003. The information was verified by the guideline developer on February 25, 2003. This summary was updated on May 3, 2005 following the withdrawal of Bextra (valdecoxib) from the market and the release of heightened warnings for Celebrex (celecoxib) and other nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI on June 16, 2005, following the U.S. Food and Drug Administration advisory on COX-2 selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI on November 22, 2006, following the FDA advisory on Effexor (venlafaxine HCl). This summary was updated by ECRI Institute on January 22, 2015. This summary was updated by ECRI Institute on September 21, 2015 following the U.S. Food and Drug Administration advisory on non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI Institute on June 2, 2016 following the U.S. Food and Drug Administration advisory on Opioid pain medicines.

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